Down's syndrome and acute lymphoblastic leukaemia: clinical features and response to treatment

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A report from the MRC childhood leukaemia working party

Abstract
***Aims*—To examine the clinical and biological features of acute lymphoblastic leukaemia in children with Down's syndrome (DS), to compare their survival with other children, and to determine if entry to trials and survival has improved.**
***Methods*—Examination of presenting features and response to treatment in patients treated in two consecutive national trials, MRC UKALL X and XI.**
***Results*—The proportion of children with DS was significantly higher in UKALL XI (1.9%) than UKALL X (0.9%). Children with DS tended to be under 10 years and to have the common ALL subtype. Cytogenetic analysis showed that favourable features, such as high hyperdiploidy and t(12;21) were less frequent but also that there was a lack of translocations associated with a poor prognosis. Children with DS showed no increase in risk of relapse at any site but their survival and event free survival were inferior to other children. These results were caused by an increased number of infective deaths during remission (11% compared to 2%). At five years overall survival was 73% in DS children compared with 82% in other children; event free survival was 53% compared to 63% in non-DS children.**
***Conclusions*—Entry of children with DS to national trials has increased and survival has improved. However they remain at risk of relapse and also of treatment related mortality. These findings emphasise the need for both intensive chemotherapy and optimal supportive care.**
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Keywords: Down syndrome; leukemia; acute lymphoblastic leukemia; chemotherapy

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Children with Down's syndrome (DS) are at increased risk of both acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML).[1] In 1990 a review of the outcome for all children with DS and ALL who were diagnosed in the UK between 1971 and 1986 found that they often received non-standard treatment and had a significantly worse prognosis than other children.[2] We have now examined the clinical features and outcome for those children with DS and ALL diagnosed between 1985 and 1997 and treated on Medical Research Council ALL trials to determine whether their outlook, like those for children with DS and AML,[3 4] has improved.

Patients and methods

We have analysed the outcome for children with DS and ALL who were treated on two consecutive UK protocols (MRC UKALL X and XI) between 1985 and 1997 and compared their clinical features and outcome with children without DS (non-DS).

Details of the two protocols have already been published; table 1 outlines the main features of both. Patients in UKALL X (1985–90)[5] all received daunorubicin as well as prednisolone, vincristine, and asparaginase during induction therapy and were randomised to receive no, one, or two blocks of intensification therapy. All children received CNS directed treatment with cranial irradiation and a course of intrathecal methotrexate.

UKALL XI (1990–97)[6] originally included randomisation in respect of one versus two intensification blocks, but was modified in 1991 so that all patients received two blocks. Further modification was introduced in 1992 (XI 92), with the omission of daunorubicin in induction and the introduction of randomisation in respect of a third prolonged intensification block.[7] Children in UKALL XI and XI92 with an initial leucocyte count of less than 50×10^9/l were randomly assigned to receive a course of intrathecal methotrexate injections and then regular intrathecal methotrexate therapy throughout treatment or additional high dose intravenous methotrexate, while those with a higher count were randomised to cranial irradiation and a course of intrathecal methotrexate or high dose intravenous methotrexate and continuing intrathecal methotrexate.

Immunophenotyping of the leukaemia was performed locally, with a recommended panel of monoclonal antibodies and central review of the results.[8] The leukaemias were classified as early pre-B (CD 10 negative), common/pre-B, and T-ALL. Cytogenetics were also performed locally and in UKALL X the results were reviewed by a reference panel,[9] whereas in UKALL XI all results were reviewed at the Leukaemia Research Fund Database.[10]

Differences in clinical features, cytogenetics, and remission rate between DS and non-DS patients were analysed using Fisher's exact test (in 2×2 tables). The Mantel–Haenszel test was used to determine trend in age and leucocyte count at presentation. Kaplan–Meier life tables were constructed for survival data and were

Table 1 Outline of treatment in MRC UKALL X and XI

Time	*Treatment phase*	*UKALL X*	*UKALL XI*	*XI-92 amendment*
Weeks 1–4	Induction	Daunorubicin days 1 and 2, prednisolone, vincristine, intrathecal methotrexate, L-asparaginase	Same as UKALL X	No daunorubicin
Weeks 5–8	First intensification	Daunorubicin, vincristine, cytarabine, etoposide, and thioguanine for a 5 day course (regimens B and D)	Half randomised as in UKALL X regimen D. All had first intensification after May 1991	All patients had first intensification
Weeks 9–12	CNS directed therapy	Cranial irradiation 18 Gy and course of intrathecal methotrexate	High risk patients randomised between cranial irradiation plus intrathecal MTX versus regular intrathecal MTX plus high dose IV MTX. Randomisation between regular intrathecal MTX alone versus additional high dose IV MTX for other patients	
Weeks 13–104	Continuing treatment	Daily mercaptopurine, weekly methotrexate, monthly prednisolone and vincristine	Same as in UKALL X with intrathecal MTX every 12 weeks for children not receiving cranial irradiation	
Weeks 20–24	Second intensification	Same as first intensification (regimens C and D)	All patients received second intensification	
Weeks 35–42	Third intensification	Not applicable	Not applicable	Dexamethasone, vincristine, L-asparaginase, cyclophosphamide, cytarabine, and thioguanine, intrathecal methotrexate

Table 2 Comparison of clinical features in children with DS and non-DS patients

Clinical feature	*Total*	*DS (%)*	*Non-DS (%)*	*p value*
Total	3651	55	3596	
Sex				
Male	2081	33 (60)	2048 (57)	
Female	1570	22 (40)	1548 (43)	NS
Age (y)				
0–1	314	2 (4)	312 (9)	
2–9	2805	51 (93)	2754 (77)	
10+	532	2 (4)	530 (15)	0.05
WBC ($\times 10^9$ /l)				
<20	2272	33 (60)	2239 (62)	
20–49	591	9 (16)	582 (16)	
50–99	335	10 (18)	325 (9)	
⩾100	453	3 (5)	450 (13)	NS
CNS involvement				
Yes	59	1 (2)	58 (2)	
No	3592	54 (98)	3538 (98)	NS
Immunophenotype				
T-ALL	343	0 (0)	343 (10)	
C/pre-B	2941	48 (87)	2893 (80)	
Null	124	0 (0)	124 (3)	0.01*

*T-ALL *v* Null/C/pre-B.

compared by means of the log rank test[11] with surviving patients being censored on 31 October 2000 (UKALL XI) or 31 October 1998 (UKALL X), when follow up was complete for the vast majority of patients. The small number of patients lost to follow up are censored at the date they were last known to be alive.

Table 3 Comparison of cytogenetic features in DS and non-DS patients

Feature	*Total with data*	*DS (%)**	*Non-DS (%)**	*p value*
Total	2465	39	2426	
Ploidy				
Near-haploid	7	0 (0)	7 (<1)	
Hypodiploid	151	2 (5)	149 (6)	
Pseudodiploid	626	7 (18)	619 (26)	
Normal	618	17 (44)	601 (25)	
HEL	281	11 (28)	270 (11)	
HEH	720	2 (5)	718 (30)	
Near triploid	30	0 (0)	30 (1)	
Near tetraploid	26	0 (0)	26 (1)	
HEH				
Yes	776	2 (5)	774 (32)	
No	1683	37 (95)	1646 (68)	<0.001
t(9;22)				
Yes	36	0 (0)	36 (1)	
No	2429	39 (100)	2390 (99)	NS
t(1;19)				
Yes	62	0 (0)	62 (3)	
No	2403	39 (100)	2364 (97)	NS
t(4;11)				
Yes	24	0 (0)	24 (1)	
No	2441	39 (100)	2402 (99)	NS
Abn 9p				
Yes	167	3 (8)	164 (7)	
No	2298	36 (92)	2262 (93)	NS
Abn 12p				
Yes	240	2 (5)	238 (10)	
No	2225	37 (95)	2188 (90)	NS
TEL/AML1				
Yes	128	1 (6)	127 (20)	
No	524	15 (94)	509 (80)	NS

*Percentage with cytogenetic data except TEL/AML1 which is % tested.
HEL, hyperdiploid, 47–49 chromosomes; HEH, high hyperdiploid, 50–59 chromosomes.

Results

CLINICAL FEATURES

Information about the presence of DS was available for 3651 (98.6%) of the 3702 patients entered into the trials and all comparative analysis has been confined to these patients. There were 55 children with DS in the two trials, significantly more in UKALL XI with 40 (1.9%) of the 2057 entrants than in UKALL X with 15 (0.9%) of 1594 children ($p = 0.01$).

Further confirmation of this improved entry was obtained by analysis of children with leukaemia notified to the Childhood Cancer Research Group during the time of these two trials. Between 1985 and 1990, 39% (14/36) of children with DS and ALL were entered on the UKALL trials while in 1991–96, 74% (39/56) were entered—a substantial and statistically significant difference ($p < 0.01$) (unpublished data from the National Registry of childhood tumours).

Table 2 shows the clinical features and immunophenotype at presentation of children with and without DS. There is no significant difference in the proportion of males and females, or the distribution of leucocyte counts at presentation. The majority of children with DS were in the 2–9 year age group; there were no infants under 1 year with DS and only two aged 10 years or more.

Examination of immunophenotype showed that all children with DS had the common or pre-B (CD10/CD 19 positive) phenotype—there were no cases of T or early pre-B (CD 10 negative/CD19 positive) ALL.

Table 3 shows the results of cytogenetics. Significantly fewer children with DS had high hyperdiploid ALL (⩾50 chromosomes). A number of the most common specific cytogenetic abnormalities such as t(9;22), t(4;11), and t(1;19) were not found in the DS group. The results of analysis for TEL/AML1, the most common genetic abnormality in acute lymphoblastic leukaemia, were only available in

Table 4 Causes of treatment failure and comparative survival at 5 years in DS and non-DS patients

Events	DS (n = 55)		Non-DS (n = 3596)		p value
	Number of events (%)	Outcome at 5 years, % (95% CI)	Number of events (%)	Outcome at 5 years, % (95% CI)	
Event free survival	27 (49%)	53% (39–66%)	1401 (39%)	63% (61–65%)	0.1
Survival	21 (38%)	73% (61–84%)	799 (22%)	82% (81–83%)	0.007
No remission	1 (2%)	Not applicable	50 (1%)	Not applicable	NS
Death in remission	6 (11%)	11% (3–20%)	88 (2%)	3% (2–3%)	<0.001
Any relapse	20 (37%)	40% (26–54%)	1263 (36%)	35% (33–36%)	NS
Isolated CNS relapse	2 (4%)	4% (0–10%)	226 (6%)	7% (6–8%)	NS
Any CNS relapse	8 (15%)	18% (7–30%)	434 (12%)	13% (12–14%)	NS
Isolated BM relapse	10 (19%)	22% (9–35%)	593 (17%)	18% (17–19%)	NS
Any BM relapse	18 (33%)	37% (23–51%)	900 (25%)	26% (25–28%)	NS

NS, p > 0.1.

652 patients with known DS status, and the abnormality was found in only one of the 16 DS children tested and in 20% of the non-DS children.

RESPONSE TO TREATMENT

Table 4 compares the absolute number of events (relapses and deaths) in children with and without DS and the incidence of these events at five years. At the time of follow up, 49% of children with DS had suffered adverse events and 38% had died. One child with DS died from *E coli* septicaemia during induction therapy (a UKALL X patient). Six children died in remission, one shortly after induction with typhlitis. Four deaths were associated with intensification therapy and two of these were caused by candida infection. One patient had combined pneumocystis and candida infection. The proportion of remission deaths was significantly higher in children with DS than the others (p < 0.001) but there were no significant differences in overall relapses, isolated or combined CNS relapses, or isolated and combined marrow relapses between children with and without DS.

Fifteen children with DS were randomised on UKALL XI to receive three intravenous methotrexate infusions. Thirteen received all three courses of methotrexate, nine without any complications. Two children developed minor infections between the second and third courses: one developed perianal blistering after the third course, and one developed neutropenia and *E coli* sepsis after the third course. Two children only received two methotrexate infusions, one having a transient encephalopathy and one a transitory right hemiparesis and dysphasia seven days after the second infusion.

The event free survival (EFS) for DS children is non-significantly inferior to that of non-DS children (2p = 0.1, fig 1). The EFS (95% confidence interval) for children with DS is 53% (39–66%) at five years compared with 63% (61–65%) for all the others. Only a small number of children with DS have been followed up beyond that time, but one late marrow relapse has been observed at over eight years from diagnosis. There have been seven relapses after eight years in the non-DS group (three isolated marrow, one combined marrow and testis, one combined marrow and CNS, one CNS, and one isolated testicular relapse); two patients died in remission, one from a second malignancy (primitive neuroectodermal tumour) and one from late complications of high dose therapy and bone marrow transplantation.

Figure 2 shows overall survival for the two groups, with DS children having a poorer prognosis (2p = 0.007). At five years survival is 73% (61–84%) in children with DS and 82% (81–83%) for the other children.

Formal tests of whether the gap in outcome between DS and non-DS children is different in UKALL X compared with UKALL XI were marginally significant (p = 0.02 for EFS; p = 0.03 for overall survival). In UKALL X DS children have a significantly worse prognosis than non-DS children for both event free (p = 0.01) and overall survival (p < 0.001). However, in UKALL XI outcome for DS children is improved and the event free and overall survival differences between DS and non-DS

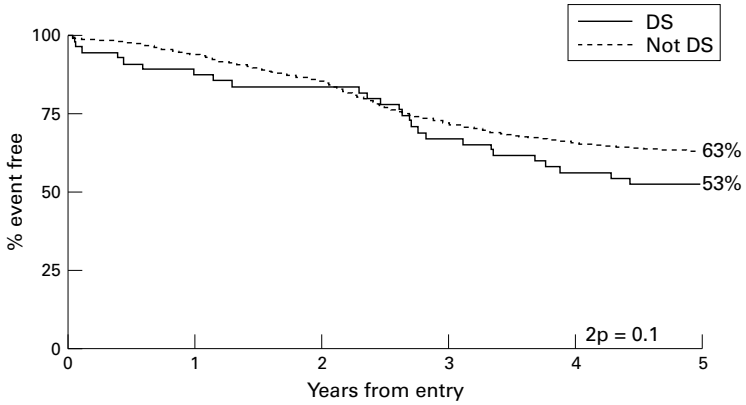

Figure 1 Event free survival comparing children with DS and others.

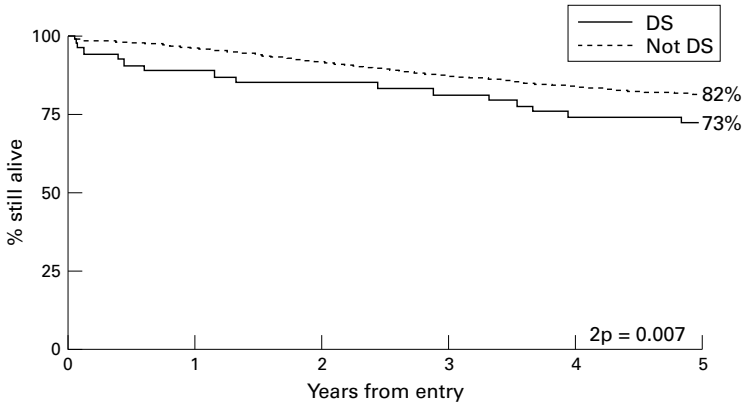

Figure 2 Overall survival in the same two groups of patients.

children are much smaller and non-significant ($p = 0.8$ and $p = 0.1$ respectively). The relative improvement in outcome for DS children appears to be caused by a reduction in the risk of both death in remission and bone marrow relapse (especially isolated marrow relapse). In UKALL X, three (21%) DS children died in remission and five (36%) had an isolated bone marrow relapse; in the later UKALL XI trial these figures were three (8%) and five (13%) respectively.

Discussion

These results confirm the typical clinical and biological features of ALL in association with DS and show that the results of treatment have improved, although problems with management remain.

Our previous study[2] of DS and ALL examined the survival of children registered with the Childhood Cancer Research Group from 1971 to 1986. Twenty four of the 61 patients either received no therapy or minimal treatment. The remainder were treated with standard protocols, but with many modifications. The five year survival was 28% (95% CI 14.2–42.6%) overall; no child in the minimally treated group survived in remission while 24% of the others remained in first remission at a follow up of two to nine years.

The present study is based on children who have been entered into national trials and shows that relatively more children with DS have been entered into the more recent UKALL XI trial. The proportion of children with DS in this trial (1.9%) is now comparable with that reported in other series.[12–14] This finding suggests that there has been increased acceptance in the UK of the need for standardised treatment in children with DS and ALL, as for those with AML. Nevertheless data from the Childhood Cancer Research Group show that one quarter of children are still not entered into trials—the comparable figure for other children is 10–15%.

We observed a significant difference in the age distribution of patients with and without DS. Few DS children presented over 10 years of age, a finding confirmed by population based studies.[1] No child with DS was under 1 year at diagnosis; none had early pre-B ALL or leukaemia in association with the t(4;11). This is not a reflection of bias in ascertainment as infants under 1 year were eligible for treatment on UKALL X and no children with DS and ALL have been entered into the MRC infant protocol, which was open to entry during the time of UKALL XI. The infrequency of ALL under 1 year of age, and the lack of early pre-B ALL has been noted in other series of patients.[14] No children with DS in the present series had T-ALL, thus confirming our previous observation,[2] and that of others[15] that ALL in children with DS is almost exclusively a disease of pre-B cells.

Information about cytogenetics was available in 39 of the DS patients. The main significant finding, as reported by others[14 15] was that fewer children with DS had high hyperdiploid ALL. In this small series of patients there were no cases of the more common non-random translocations, t(9;22), t(1;19), and t(4;11), although other common abnormalities such as abnormal 9p and 12p were observed. Absence of the more common translocations was noted in a combined series of children with DS from St Jude Children's Hospital and the Paediatric Oncology Group.[15]

Abnormalities of chromosome 21 are commonly found in the leukaemic cells of children with ALL. Indeed the most common cytogenetic finding in paediatric ALL is the cryptic t(12;21) involving the *TEL* gene on chromosome 12p13 and the *AML1* gene on chromosome 21q22. This translocation has been found in 16–36% of cases of paediatric ALL[16] and in some reports it is associated with a favourable response to treatment. The t(12;21) was found in 20% of 637 non-DS samples tested but in only one of the 16 with DS. This low incidence concords with the results of a small retrospective study by Lanza and colleagues[17] where none of a series of 11 patients with DS and ALL had the rearrangement. These findings suggest that, despite the fact that the AML1 gene is involved in the critical DS region of chromosome 21,[18] alternative mechanisms may be involved in the development of leukaemia.

Children with DS and ALL tend to lack both favourable and adverse prognostic factors and it appears that their risk of relapse is similar to that of others. A large early study from the American Children's Cancer Group[12] found that children with DS had a lower induction rate but similar disease free survival to other children. A report from the Paediatric Oncology Group evaluated outcome according to treatment intensity and found no difference in outcome between DS and non-DS children among more intensively treated patients.[13] A more recent publication combined data from this group with that from St Jude Children's research hospital and failure in DS was largely caused by treatment related toxicity.[15] Modifications of treatment were made in 43% of children with DS and ALL treated by the Berlin–Frankfurt–Munster group; these children had a worse event free survival than those without treatment modifications.[14]

Our results show that both event free survival and overall survival for children with DS have improved in comparison with the previous survey from the UK. The five year survival of 28% (95% CI 14–43%) observed in the previous study has improved to 73% (61–84%), but remains inferior to that of other children. Event free survival was also inferior although not significantly so, and the pattern of relapses was similar in DS and non-DS patients. The difference in outcome in our population was mainly caused by remission deaths rather than relapse at any site and although there has been an overall reduction in the numbers of deaths in remission in the most recent UKALL XI trial, the rate in DS children is still higher than in non-DS children.

Children with DS are known to be vulnerable to infection and when treated for ALL show unusual sensitivity to methotrexate.[19] We

have not formally compared the toxicity experienced by the DS children in UKALL XI with the non-DS group but the majority of patients experienced no undue toxicity during high dose methotrexate, perhaps because of the schedule and rigid instructions for folinic acid rescue.

A more detailed analysis of mortality in UKALL X[20] and UKALL XI[21] has confirmed that DS is significantly associated with risk of infective deaths, particularly during intensification after remission induction. It is notable that three of the deaths in the DS children were associated with candida infection. The balance between giving sufficiently intensive treatment and avoiding excess morbidity and mortality is a difficult one. Our results and those of others emphasise the need for careful supervision of these children during treatment, prompt management of suspected infection, and early instigation of antifungal therapy. Efforts should be made to minimise modifications of therapy, as the major risk of treatment failure now, as in previous protocols, remains leukaemic relapse.

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1 Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. *Lancet* 2000;**355**:165–9.
2 Levitt GA, Stiller CA, Chessells JM. Prognosis of Down's syndrome with acute leukaemia. *Arch Dis Child* 1990;**65**: 212–16.
3 Craze JL, Harrison G, Wheatley K, *et al*. Improved outcome of acute myeloid leukaemia in Down's syndrome. *Arch Dis Child* 1999;**81**:32–7.
4 Lange B. The management of neoplastic disorders of haematopoiesis in children with Down's syndrome. *Br J Haematol* 2000;**110**:512–24.
5 Chessells JM, Bailey C, Richards SM. Intensification of treatment and survival in all children with lymphoblastic leukaemia: results of UK Medical Research Council trial UKALL X. *Lancet* 1995;**345**:143–8.
6 Richards S, Burrett J, Hann IM, *et al*. Improved survival with early intensification: combined results from the Medical Research Council Childhood ALL randomised trials, UKALL X and XI. *Leukaemia* 1998;**12**:1301–6.
7 Hann I, Vora A, Richards S, *et al*. Benefit of intensified treatment for all children with acute lymphoblastic leukaemia: results from MRC UKALL XI and MRC ALL97 randomised trials. UK Medical Research Council's Working Party on Childhood Leukaemia. *Leukemia* 2000; **14**:356–63.
8 Hann IM, Richards SM, Eden OB, Hill FGH. Analysis of the immunophenotype of children treated on the Medical Research Council (MRC) United Kingdom acute lymphoblastic leukaemia trial XI (UKALL XI). *Leukaemia* 1998;**12**:1249–55.
9 Chessells JM, Swansbury GJ, Reeves B, *et al*. Cytogenetics and prognosis in childhood lymphoblastic leukaemia: results of MRC UKALL X. *Br J Haematol* 1997;**99**:93–100.
10 Hann I, Vora A, Harrison C, *et al*. Determinants of outcome after intensified therapy of childhood lymphoblastic leukaemia; results from Medical Research Council United Kingdom acute lymphoblastic leukaemia XI protocol. *Br J Haematol* 2001;**113**:103–14.
11 Peto R, Pike MC, Armitage P, *et al*. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II Analysis and examples. *Br J Cancer* 1977;**35**:1–39.
12 Robison LL, Nesbit ME, Sather HN, *et al*. Down syndrome and acute leukemia in children: a 10-year retrospective survey from Childrens Cancer Study Group. *J Pediatr* 1984;**105**:235–42.
13 Ragab AH, Abdel-Mageed A, Shuster JJ, *et al*. Clinical characteristics and treatment outcome of children with acute lymphocytic leukemia and Down's syndrome. A Pediatric Oncology Group study. *Cancer* 1991;**67**:1057–63.
14 Dordelmann M, Schrappe M, Reiter A, *et al*. Down's syndrome in childhood acute lymphoblastic leukemia: clinical characteristics and treatment outcome in four consecutive BFM trials. Berlin-Frankfurt-Munster Group. *Leukemia* 1998;**12**:645–51.
15 Pui C-H, Raimondi SC, Borowitz MJ, *et al*. Immunophenotypes and karyotypes of leukemic cells in children with Down syndrome and acute lymphoblastic leukemia. *J Clin Oncol* 1993;**11**:1361–7.
16 Rubnitz JE, Pui C-H, Downing JR. The role of TEL fusion genes in pediatric leukemias. *Leukemia* 1999;**13**:6–13.
17 Lanza C, Volpe G, Basso A, *et al*. The common TEL/AML1 rearrangement does not represent a frequent event in acute lymphoblastic leukaemia occuring in children with Down syndrome. *Leukemia* 1997;**11**:820–1.
18 Legare RD, Lu D, Gallagher M, *et al*. CBFA2, frequently rearranged in leukemia, is not responsible for a familial leukemia syndrome. *Leukemia* 1997;**11**:2111–19.
19 Garre ML, Relling MV, Kalwinsky D, *et al*. Pharmacokinetics and toxicity of methotrexate in children with Down syndrome and acute lymphocytic leukemia. *J Pediatr* 1987; **111**:606–12.
20 Wheeler K, Chessells JM, Bailey CC, Richards SM. Treatment related deaths during induction and in first remission in acute lymphoblastic leukaemia: MRC UKALL X. *Arch Dis Child* 1996;**74**:101–7.
21 Hargrave DR, Hann IM, Richards SM, *et al*. Progressive reduction in treatment related deaths in MRC Childhood Lymphoblastic Leukaemia trials from 1980 to 1997 (UKALL VIII, X and XI). *Br J Haematol* 2001;**112**:293–9.